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MAJOR ARTICLE

Cost Effectiveness and Cost Containment in the Era of Interferon-Free Therapies to Treat Hepatitis C Virus Genotype 1

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Background. Interferon-free regimens to treat hepatitis C virus (HCV) genotype 1 are effective but costly. At this time, payers in the United States use strategies to control costs including (1) limiting treatment to those with advanced disease and (2) negotiating price discounts in exchange for exclusivity.

Methods. We used Monte Carlo simulation to investigate budgetary impact and cost effectiveness of these treatment policies and to identify strategies that balance access with cost control. Outcomes included nondiscounted 5-year payer cost per 10 000 HCV-infected patients and incremental cost-effectiveness ratios.

Results. We found that the budgetary impact of HCV treatment is high, with 5-year undiscounted costs of $1.0 billion to 2.3 billion per 10 000 HCV-infected patients depending on regimen choices. Among noncirrhotic patients, using the least costly interferon-free regimen leads to the lowest payer costs with negligible difference in clinical outcomes, even when the lower cost regimen is less convenient and/or effective. Among cirrhotic patients, more effective but costly regimens remain cost effective. Controlling costs by restricting treatment to those with fibrosis stage 2 or greater disease was cost ineffective for any patient type compared with treating all patients.

Conclusions. Treatment strategies using interferon-free therapies to treat all HCV-infected persons are cost effective, but short-term cost is high. Among noncirrhotic patients, using the least costly interferon-free regimen, even if it is not single tablet or once daily, is the cost-control strategy that results in best outcomes. Restricting treatment to patients with more advanced disease often results in worse outcomes than treating all patients, and it is not preferred.

Keywords. budget impact; HCV; treatment restriction.

New medications to treat hepatitis C virus (HCV) are costly, with wholesale acquisition costs exceeding $1000/day in the United States [1]. Several recent cost-effectiveness analyses concur that even at such high prices, all oral sofosbuvir-based regimens to treat HCV genotype 1 (GT1) provide good value compared with the previous standard of care [2–6]. Given that there are 2–3 million HCV-infected people in the United States [7], however, the budget impact of providing new HCV treatments to all who need them could exceed the healthcare system's ability to pay, despite attractive cost-effectiveness ratios [2–4]. As multiple interferon-free regimens enter the market, payers negotiate with pharmaceutical manufacturers covering 1 exclusive interferon-free treatment regimen in exchange for substantial price discounts, potentially trading efficacy for lower cost [8]. Many insurers further limit access to new HCV therapies by prioritizing patients with higher degrees of liver fibrosis for treatment, although there is no consensus on this threshold with thresholds ranging from fibrosis stage 2 (F2) to F4 [9]. Because these restrictions are recent inventions, data are needed to inform decision making and to shed light on the relative costs and benefits of different approaches to controlling HCV treatment costs.

In this environment—where alternative treatment options are both highly efficacious and costly—it is particularly important to understand the budgetary impact and economic value of new treatments as well as to identify approaches to expand access while controlling cost. We used the Hepatitis C Cost-Effectiveness (HEP-CE) Model [10, 11] to consider the policy questions that payers currently face when considering coverage of high-cost HCV medications in the competitive US market including the following: (1) how much to budget for every 10 000 HCV-infected patients within a jurisdiction or health plan, (2) how to make cost-effective trade-offs between efficacy and cost, and (3) whether to contain costs by limiting access to only those with F2 or greater.

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METHODS

Overview

The HEP-CE Model is a Monte Carlo lifetime simulation of HCV infection, screening, and treatment, summarized briefly below and in greater detail in the Supplementary Materials and published literature [10, 11]. We constructed the model and performed analyses using TreeAge Pro software (TreeAge Software, Inc., Williamstown, MA).

We assumed the health system perspective on treatment costs for HCV GT1 in patients who are engaged in care and prepared to initiate HCV therapy. We considered distinct patient types defined by GT1 subtype (1a vs 1b), fibrosis stage (noncirrhotic vs cirrhotic), treatment history (naive vs experienced), and ribonucleic acid (RNA) level for treatment-naive, noncirrhotic patients (<6 million copies vs ≥6 million copies) (Table 1). Each of these patient types was associated with a distinct menu of treatment options (Table 1) and related sustained virologic response (SVR). We did not evaluate treatment of decompensated cirrhosis.

We used the model to simulate clinical outcomes and costs for hypothetical cohorts of 1 million patients for each patient type and treatment strategy. Outcomes included the following: quality-adjusted life years (QALYs) and lifetime medical costs, each discounted at 3% annually [12], and the 5-year, undiscounted budgetary impact per 10 000 HCV-infected patients [13]. To estimate the 5-year budget impact, we ran the model for 5 simulated years to estimate mean undiscounted cost per patient. We then multiplied that 5-year mean cost by 10 000 to estimate the total budget impact. We chose a 5-year horizon because that is a time period of relevance to payers [13]. We express budget impact in terms of cost/10 000 because that quantity can be scaled up or down by payers to estimate budgetary impact for their specific populations. We calculated the incremental cost-effectiveness ratio (ICER) for each strategy by dividing the additional lifetime cost by the additional QALYs gained compared with the next less expensive strategy [12]. We deemed regimens that provided lower QALYs at higher total cost than an alternative, as well as regimens that provided fewer QALYs at a higher cost per QALY gained, to be inefficient (dominated), and we excluded them from the final comparisons [12].

We next modeled a scenario in which noncirrhotic patients could be treated for HCV only when they reached METAVIR F2 or greater (F2+ only). Because of the large potential number of strategies when considering all regimens and treatment restrictions a priori, we developed an approach to incorporating the "treat F2+ only" approach. First, we identified the preferred interferon-free regimen for a given patient type assuming the "treat-all" approach. We then considered the "F2+ only" strategy only for the preferred treatment regimen. In addition, because the quality of life (QoL) of patients with early stage HCV infection is uncertain, and this value can affect the cost effectiveness of early HCV therapy, we included a scenario in which patients with early HCV had a much higher QoL than they did in the base case analysis.

Finally, we performed a series of sensitivity analyses in which we varied the efficacy and cost of one interferon-free regimen, while holding constant the efficacy and cost of all others. We report the relationships between relative efficacy, cost, and cost effectiveness using 2-way sensitivity analysis graphs [12].

We performed extensive deterministic and probabilistic sensitivity analyses. A priori parameters of interest included treatment efficacy, treatment cost, fibrosis staging test characteristics (sensitivity and specificity of correctly identifying a given stage), QoL with early HCV, mean age of the population, and QoL after SVR. We performed 2-way sensitivity analyses in which we considered various combinations of rates of fibrosis progression and QoL with early disease. We summarize sensitivity analysis results using one-way graphs and cost-effectiveness acceptability curves.

Table 1. Treatment Strategies Considered in a Cost-Effectiveness Analysis of Therapies for HCV Genotype 1 Infection

Treatment History	Noncirrhotic	Cirrhotic
Treatment-naive	48 weeks pegylated-interferon/ribavirin 24 weeks simeprevir/pegylated-interferon/ribavirin 12 weeks sofosbuvir/pegylated-interferon/ribavirin 8 weeks sofosbuvir/ledipasvir (HCV RNA <6 million) 12 weeks sofosbuvir/ledipasvir (HCV RNA ≥6 million) 12 weeks paritaprevir-ritonavir/ombitasvir/dasabuvir /(ribavirin)[a] 12 weeks daclatasvir/sofosbuvir	48 weeks pegylated-interferon/ribavirin 24 weeks simeprevir/pegylated-interferon/ribavirin 12 weeks sofosbuvir/pegylated-interferon/ribavirin 12 weeks sofosbuvir/ledipasvir 12 weeks paritaprevir-ritonavir/ombitasvir/dasabuvir/ribavirin 24 weeks daclatasvir/sofosbuvir
Treatment-experienced	12 weeks sofosbuvir/pegylated-interferon/ribavirin 12 weeks simeprevir/sofosbuvir 12 weeks sofosbuvir/ledipasvir 24 weeks sofosbuvir/ledipasvir 12 weeks paritaprevir-ritonavir/ombitasvir/dasabuvir/ribavirin 12 weeks daclatasvir/sofosbuvir	12 weeks sofosbuvir/pegylated-interferon/ribavirin 12 weeks simeprevir/sofosbuvir 12 weeks sofosbuvir/ledipasvir/ribavirin 24 weeks sofosbuvir/ledipasvir 12 to 24 weeks paritaprevir-ritonavir/ombitasvir/dasabuvir/ribavirin[b] 24 weeks daclatasvir/sofosbuvir/ribavirin

Abbreviations: HCV, hepatitis C virus; RNA, ribonucleic acid.

[a]Ribavirin is included for genotype 1a and not for 1b patients.

[b]Twelve weeks for 1b patients, 24 weeks regimen for genotype 1a patients.

Model Structure

Hepatitis C Virus Disease Progression

The simulation includes 3 stages of liver disease: mild to moderate fibrosis, cirrhosis, and decompensated cirrhosis; the rate of progression varies among simulated patients, and the model operationalizes this variation by randomly drawing the time from the date of HCV infection to that of developing cirrhosis so that at model start an individual's fibrosis stage is a function of their age, age of infection, and fibrosis progression (see Supplementary Appendix for details). For F2+ only strategies, we considered simulated patients to have reached F2 disease when they had accrued 50% of their total time from HCV infection to cirrhosis.

At every disease stage, HCV infection is associated with higher costs and lower QoL compared with HCV-uninfected individuals [14–16] (Table 2). When patients reach cirrhosis, they are subject to HCV-attributable mortality. The rate of HCV-attributable mortality further increases when patients reach decompensated cirrhosis, reflecting both the increasing risks posed by advanced liver disease such as hepatocellular carcinoma and the elevated mortality risk of extrahepatic conditions such as esophageal varices [17].

Competing Causes of Death

In every month, individuals in the model are exposed to age- and sex-stratified risk of death from causes other than HCV [18]. Because this analysis focuses specifically on HCV-infected patients who are engaged in medical care and ready to initiate HCV therapy, we assume that competing risks are similar to those of the general population, and we explore that assumption in sensitivity analyses.

Hepatitis C Virus Treatment Simulation

The probability of attaining SVR to treatment is specific to regimen and patient type, and it is a function of the probabilities of withdrawing from treatment for nonadherence or toxicity and achieving SVR conditional on completing treatment (Table 2). Patients taking pegylated-interferon/ribavirin or pegylated-interferon/ribavirin/simeprevir who have inadequate virologic response at treatment week 12 discontinue treatment [19–21]. There are no early stopping criteria for any other regimen [22–25]. We did not consider patients with previous exposure to HCV polymerase inhibitors or NS5A inhibitors.

In F2+ only strategies, noncirrhotic patients are eligible to start therapy only when their fibrosis is clinically identified. We assume annual fibrosis staging with test characteristics representative of the mean sensitivity and specificity reported for the Fibroscan and Fibrosis-4 tests (Table 2) to identify moderate fibrosis [26]. Thus, some early stage patients receive therapy, whereas other advanced patients are incorrectly delayed. We conducted a sensitivity analysis in which we assumed perfect staging.

We developed efficacy parameters using data from multiple clinical trials [19–25, 27–32]. We used a Bayesian approach to develop probability density functions around each efficacy parameter value. The expected value of each distribution matched the data reported from clinical trials, whereas the variance reflected uncertainty surrounding the data based on sample size (Supplemental Tables 1 and 2).

Costs

We denominate costs in 2014 US dollars, and when necessary input costs were inflated to 2014 dollars using the consumer price index. In each simulation month, individuals accrue non-HCV-related costs based on age and sex (Table 2) [33]. Monthly costs related to HCV increase with advancing disease due to the increasing risk of liver disease sequelae such as hepatocellular carcinoma and liver transplantation as well as extrahepatic manifestations of HCV [34]. Because HCV-related costs are variable across patients, we estimate probability density functions around these costs using the gamma distribution. We then assign each simulated patient a disease stage-specific monthly HCV-related cost by random draw from those distributions (Table 2).

The costs of HCV therapy include costs of HCV medications, clinic visits, laboratory tests, and on-treatment toxicity management (Table 2, Supplemental Table 3). We assume that the cost of HCV therapies includes the medication discount available to public payers such as Medicaid plans, which we model as the average wholesale price (AWP) less 23% [1, 35]. Due to the rapid evolution in the HCV treatment market, competitive negotiation, and price discounts, we performed extensive sensitivity analyses on medication cost.

Quality-of-Life

Quality-of-life reflects the combination of 3 utility functions: (1) utility related to non-HCV comorbidities, which is a function of age [36]; 2) HCV-specific utility, which is a function of fibrosis stage [14–16]; and (3) treatment-related utility, reflecting lower QoL on interferon-containing regimens as well as major toxicity events on treatment in all regimens [37–39]. In addition, because the QoL with early stage HCV is uncertain and has a potentially large impact on the cost-effectiveness of early HCV therapy, we included a scenario in which early stage HCV is assigned a QoL weight of 0.95 [6, 14, 40]. We assumed that effects of each of these utility functions on total utility are independent and proportional.

Benefits of Sustained Virologic Response

When patients attain SVR, fibrosis progression halts, HCV-attributable costs are reduced to 50% of an individual's disease stage-specific cost before initiating therapy [34], and QoL reverts to that of HCV-uninfected individuals of the same age and sex [37]. In individuals who were cirrhotic before attaining SVR, liver-related mortality decreases by 94% [41].

Table 2. Model Inputs for a Cost-Effectiveness Analysis of Strategies for Cost Containment in Provision of Interferon-Free Therapy for HCV Genotype 1

Variable	Base Case Value	Range Evaluated in Sensitivity Analyses[a]	Source(s)
Cohort Characteristics			
Mean age treatment-naive (SD), years	52 (14)	42 (14)–62 (14)	[23]
Mean age treatment-experienced (SD), years	56 (14)	46 (14)–66 (14)	[22]
Proportion male (treatment-naive)	0.59	0–1	[23]
Proportion male (treatment-experienced)	0.68	0–1	[22]
Average age at HCV infection, years	26	16–36	[34]
HCV Disease Progression			
Median time to cirrhosis from time of HCV infection, years	25	10–40	[48, 49]
Median time to first liver-related event after developing cirrhosis, years	11	6–19	[17]
Liver-related mortality with compensated cirrhosis, deaths/100 PYs	1.39	0.96–1.82	[17]
Liver-related mortality with decompensated cirrhosis, deaths/100 PYs	12.00	8.28–15.72	[17]
Reduction in liver-mortality after SVR, %[b]	94	81–98	[41]
HCV Therapy Efficacy, Treatment-Naive[c]			
SVR probabilities for 48 weeks pegylated-interferon/ribavirin			[19]
Genotype 1 without cirrhosis	0.44	0.44 (0.02)	
Genotype 1 with cirrhosis	0.24	0.23 (0.04)	
SVR probabilities for 24 weeks pegylated-interferon/ribavirin/simeprevir			[20, 21]
Genotype 1a without cirrhosis	0.78	0.77 (0.03)	
Genotype 1a with cirrhosis	0.55	0.53 (0.10)	
Genotype 1b without cirrhosis	0.91	0.89 (0.02)	
Genotype 1b with cirrhosis	0.65	0.63 (0.10)	
SVR probabilities for 12 weeks pegylated-interferon/ribavirin/sofosbuvir			[32]
Genotype 1 without cirrhosis	0.92	0.92 (0.02)	
Genotype 1 with cirrhosis	0.80	0.79 (0.05)	
SVR probability for 8 weeks sofosbuvir/ledipasvir			[28, 50]
Genotype 1 without cirrhosis	0.97	0.96 (0.02)	
SVR probability for 12 weeks sofosbuvir/ledipasvir			[28, 50]
Genotype 1 without cirrhosis	0.96	0.96 (0.02)	
Genotype 1 with cirrhosis	0.97	0.95 (0.04)	
SVR probability for 12 weeks paritaprevir-ritonavir/ombitasvir/dasabuvir ± ribavirin			[29, 31]
Genotype 1a without cirrhosis (with ribavirin)	0.97	0.97 (0.02)	
Genotype 1a with cirrhosis (with ribavirin)	0.92	0.91 (0.04)	
Genotype 1b without cirrhosis (without ribavirin)	0.99	0.98 (0.01)	
Genotype 1b with cirrhosis (with ribavirin)	0.99	0.97 (0.03)	
SVR probability for 12 or 24 weeks of daclatasvir/sofosbuvir			
Genotype 1 without cirrhosis (12 weeks)	0.99	0.99 (0.01)	[25]
Genotype 1 with cirrhosis (24 weeks)	0.99	0.99 (0.01)	[27]
HCV Therapy Efficacy, Treatment-Experienced[c]			
SVR probability for 12 weeks pegylated-interferon/ribavirin/sofosbuvir			[32]
Genotype 1 without cirrhosis	0.92	0.92 (0.02)	
Genotype 1 with cirrhosis	0.80	0.78 (0.06)	
SVR probability for 12 or 24 weeks of sofosbuvir/ledipasvir			[22]
Genotype 1 without cirrhosis (12 weeks)	0.95	0.95 (0.02)	
Genotype 1 with cirrhosis (24 weeks)	0.99	0.97 (0.02)	
SVR probabilities for 12 or 24 weeks paritaprevir-ritonavir/ombitasvir/dasabuvir/ribavirin			[30, 31]
Genotype 1a without cirrhosis (12 weeks)	0.96	0.96 (0.02)	
Genotype 1a with cirrhosis (24 weeks)	0.95	0.94 (0.02)	
Genotype 1b without cirrhosis (12 weeks)	0.97	0.96 (0.01)	
Genotype 1b with cirrhosis (12 weeks)	0.97	0.96 (0.01)	
SVR probability for 12 weeks sofosbuvir/simeprevir			[24]
Genotype 1a without cirrhosis	0.90	0.88 (0.10)	
Genotype 1a with cirrhosis	0.91	0.89 (0.08)	
Genotype 1b without cirrhosis	0.99	0.99 (0.00)	
Genotype 1b with cirrhosis	0.99	0.97 (0.01)	
SVR probability for 12 weeks of sofosbuvir/ledipasvir/ribavirin			
Genotype 1 with cirrhosis	0.96	0.94 (0.02)	[51]
SVR probability for 12 or 24 weeks of daclatasvir/sofosbuvir ± ribavirin			
Genotype 1 without cirrhosis (12 weeks without ribavirin)	0.99	0.99 (0.01)	[25]
Genotype 1 with cirrhosis (24 weeks with ribavirin)	0.98	0.97 (0.01)	[27]
Fibrosis staging (for F2+ only strategy)			[26]
FibroScan sensitivity to detect F2 or greater	0.48	0.48–1	
FibroScan specificity to detect F2 or greater	0.93	0.93–1	

Table 2. Continued

Variable	Base Case Value	Range Evaluated in Sensitivity Analyses[a]	Source(s)
Costs			
Non-HCV-related medical costs, $ per month			
Background medical costs (without HCV)[d]	$140–$1050	$70–$1575	[33]
HCV-related medical costs, $ per month			
No cirrhosis (SD)	$245 ($60)	$185 ($45)–$305 ($75)	[34]
Mild to moderate cirrhosis (SD)	$440 ($125)	$315 ($90)–$550 ($150)	[34]
Decompensated cirrhosis (SD)	$830 ($215)	$620 ($160)–$1050 ($260)	[34]
Costs multiplier after achieving SVR	0.50	0–0.70	[34]
HCV Therapy Costs, $ per 4 Weeks			
Provider visit costs[e]	$120	$60–180	[52, 53]
Pegylated-interferon[f]	$720	$370–$1200	[1]
Ribavirin[g]	$1200	$560–$1700	[1]
Sofosbuvir	$26 500	$13 000–$40 000	[1]
Sofosbuvir/ledipasvir	$29 000	$15 000–$43 000	[1]
Simeprevir	$21 000	$11 000–$32 000	[1]
Paritaprevir-ritonavir/ombitasvir/dasabuvir	$26 000	$13 000–$39 000	[1]
Daclatasvir	$19 300	$9500–$28 500	[1]
Filgrastim[h]	$2800	$1500–$5100	[1]
Complete HCV therapy costs, $			[1, 52, 53]
Pegylated-interferon/ribavirin 48 weeks	$52 600	$26 000–$79 500	
Pegylated-interferon/ribavirin/simeprevir 24 weeks	$75 000	$37 500–$113 000	
Pegylated-interferon/ribavirin/sofosbuvir 12 weeks	$91 000	$45 500–$137 000	
Sofosbuvir/ledipasvir 8 weeks	$58 200	$29 000–$88 200	
Sofosbuvir/ledipasvir 12 weeks	$87 300	$47 300–$107 300	
Sofosbuvir/ledipasvir 24 weeks	$175 000	$115 000–$215 000	
Sofosbuvir/ledipasvir/ribavirin 12 weeks	$90 600	$31 000–$112 000	
Paritaprevir-ritonavir/ombitasvir/dasabuvir 12 weeks	$77 000	$23 000–$97 000	
Paritaprevir-ritonavir/ombitasvir/dasabuvir/ribavirin 12 weeks	$80 300	$30 000–$100 300	
Paritaprevir-ritonavir/ombitasvir/dasabuvir/ribavirin 24 weeks	$161 000	$101 000–$201 000	
Sofosbuvir/simeprevir 12 weeks	$139 000	$69 500–$209 000	
Daclatasvir/sofosbuvir 12 weeks	$137 000	$68 500–$206 000	
Daclatasvir/sofosbuvir 24 weeks	$274 000	$137 000–$411 000	
Daclatasvir/sofosbuvir/ribavirin 24 weeks	$280 000	$140 000–$420 000	
One-time costs, $			
Managing treatment-ending toxicity on interferon-containing therapy	$465–$877	$360–$1200	[1, 19, 20, 32, 52–55]
Managing treatment-ending toxicity on interferon-free therapy	$241	$100–$610	[29, 52–55]
Quality of life[i]			
After achieving SVR	0.74–0.92	0.60–1	[37]
With HCV Infection			
No-to-moderate fibrosis	0.89	0.75–1	[14–16]
Cirrhosis	0.62	0.55–0.75	[14, 15]
Decompensated cirrhosis	0.48	0.40–0.60	[14, 15]
Receiving interferon-containing therapy[j]	0.88	0.50–0.96	[37, 38]
Receiving interferon-free therapy[j]	0.99	0.95–1	[38]
Major toxicity decrement[k]	0.16	0.09–0.25	[39]

Abbreviations: F2, fibrosis stage 2; HCV, hepatitis C virus; PYs, person-years; SD, standard deviation; SVR, sustained virologic response.

(NOTE: All costs are in 2014 US dollars and discounted at an annual rate of 3%.).

[a]Sensitivity analyses on HCV therapy efficacy were probabilistic as opposed to deterministic (see Methods). The table provides the approximate mean and SD of the beta distribution developed to reflect uncertainty in efficacy estimates.

[b]Because HCV-attributable mortality is only applied in the model once individuals are cirrhotic, this probability is applied only to individuals who had cirrhosis before initiating treatment and subsequently attained SVR.

[c]Efficacy estimates for patient subgroups (eg, genotype 1b treatment-naive with cirrhosis) are informed by clinical trials.

[d]Costs varied as a function of age and sex.

[e]Cost in first month is higher ($750).

[f]15% of patients on pegylated-interferon/ribavirin and sofosbuvir/pegylated-interferon/ribavirin therapy receive a reduced weekly dose of 135 mcg due to nontreatment-ending neutropenia (absolute neutrophil count <750/mL but ≥500/mL) in addition to twice weekly filgrastim 300 mcg [32].

[g]26% of patients on pegylated-interferon/ribavirin, 20% of patients pegylated-interferon/ribavirin/ sofosbuvir therapy, 23% of patients on pegylated-interferon/ribavirin/simeprevir, and 6% of patients on paritaprevir-ritonavir/ombitasvir/dasabuvir/ribavirin therapy were treated with a reduced dose of daily ribavirin in response to nontreatment-ending anemia (grade 3–4 adverse event of hemoglobin <10 g/dL) [19–21, 29].

[h]The cost of a nurse visit ($20.40) is also included for anemia management [52].

[i]Utility without HCV infection is a function of age. To estimate utility in a given month, the model uses a multiplicative assumption to combine HCV-related utility with age- and sex-stratified utility without HCV. For example, the utility estimate without HCV infection for a 55-year-old is 0.84. The estimated utility of living with compensated cirrhosis is 0.62. A 55-year-old with compensated cirrhosis would have a modeled utility of $0.84 \times 0.62 = 0.52$.

[j]This utility weight was multiplied by an individual's health state utility during the months that the individual received HCV therapy without major toxicity.

[k]This utility loss was subtracted from a patient's health state utility during the month of a major toxicity event.

RESULTS

Cost Control by Deferring Treatment Until Fibrosis Stage 2 (F2± Only)

Treating all noncirrhotic patients with an interferon-free regimen regardless of disease stage resulted in a nondiscounted 5-year payer cost in the range of $1.02 billion to $2.14 billion per 10 000 patients treated, quality adjusted life expectancy of 14.4 to 14.7 QALY per patient, and a discounted lifetime medical cost of $227 000 to $329 000 per patient. Strategies that limited access to patients with F2 or greater fibrosis had lower 5-year total cost, but strategies that treated all patients resulted in better quality-adjusted life expectancy and provided good value for money.

In all patient types, treat all strategies had economically attractive ICERs according to conventional benchmarks (ICER <$100 000/QALY), and in many patient types treat-all provided better outcomes than F2+ only at a lower cost per QALY gained (Tables 3 and 4). These findings were robust in all age groups (mean age 42 and mean age 62) and with various assumptions about rates of fibrosis progression, mortality (including doubling the risk of death from non-HCV mortality), cost, and rates of HCV reinfection after SVR (Supplemental Tables 4–15) as well as QoL (Supplemental Figure 1). When we assumed high QoL with noncirrhotic HCV infection (0.95), the qualitative conclusions did not change (Supplemental Table 16). In probabilistic sensitivity analyses, F2+ only was almost never preferred for any patient type (Figure 1).

The F2+ only approach was not preferred for several reasons. First, patients had lower QoL as liver fibrosis advances, and therefore they lost QALYs while waiting for therapy. In sensitivity analyses, treat-all strategies were preferred unless the utility weight of early stage HCV infection was >0.97 (base case 0.89) (Supplemental Figure 1). Second, most patients eventually reached F2 and were ultimately treated for HCV. For example, among GT1a, treatment-naive, noncirrhotic patients, 92% were ultimately treated for HCV. In sensitivity analysis with slower fibrosis progression rates (median time to cirrhosis = 40 years), treat all remained preferred. Only when the discount rate was greater than 10% (base case 3% in accordance with current guidelines for economic analysis) did F2+ only strategies begin to have ICERs <$100 000/QALY. Third, noninvasive fibrosis staging modalities are imperfect [26], and some patients with advanced fibrosis were inappropriately deferred. Eliminating uncertainty in fibrosis staging improved outcomes and decreased the ICER of F2+ only, but the ICER of treat all remained attractive (<$100 000/QALY) (Supplemental Table 17).

Cost Control by Negotiating Price Discounts and Requiring Use of Preferred Drugs

Noncirrhotic Patients

Among noncirrhotic patients, genotypes 1a and 1b, the choice of which interferon-free regimen to use depended on regimen cost. For example, among GT 1a and 1b treatment-naive, noncirrhotic patients with HCV RNA <6 million copies/mL, for whom sofosbuvir/ledipasvir is an 8-week regimen, sofosbuvir/ledipasvir dominated interferon-containing regimens, and the ICER of sofosbuvir/ledipasvir compared with "no treatment" was $21 700/QALY. In such patients, paritaprevir/ritonavir/ombitasvir/dasabuvir ± ribavirin was estimated to be slightly more effective than sofosbuvir/ledipasvir (97%–98% SVR vs 96% SVR), but because the 12-week paritaprevir/ritonavir/ombitasvir/dasabuvir ± ribavirin treatment course greatly increased cost relative to 8 weeks of sofosbuvir/ledipasvir, the ICER of paritaprevir/ritonavir/ombitasvir/dasabuvir ± ribavirin among treatment-naive patients with RNA <6 million copies/mL was more than $600 000/QALY gained. Likewise, in GT1a and GT1b noncirrhotic patients, sofosbuvir/daclatasvir had the highest modeled treatment efficacy, but because of its high cost, it was never preferred for noncirrhotic patients.

In two-way sensitivity analyses among noncirrhotic patients, each percentage point improvement in interferon-free regimen efficacy could support an additional cost of only $875 per month of treatment ($2625 for a 12-week course). Larger cost increases resulted in the more effective regimen having an ICER >$100 000/QALY gained compared with the less effective regimen (Figure 2).

In probabilistic sensitivity analyses, interferon-free therapy had an ICER <$100 000/QALY in >99% of simulations, with the least costly interferon-free regimen always preferred when the threshold for willingness to pay for each year of healthy life was $100 000/QALY gained (Supplemental Figure 2).

Cirrhotic Patients

Among cirrhotic patients, genotype 1a and 1b, regimen efficacy played a larger role in determining the choice of which interferon-free regimen was cost effective. In two-way sensitivity analyses, each additional percentage point of regimen efficacy could be associated with up to a $2400 increase in monthly regimen cost ($7200 for a 12-week treatment course) for the more effective regimen to remain cost effective with an ICER <$100 000/QALY (Figure 1). Even among cirrhotic patients, however, very small differences in treatment efficacy did not provide adequate improvement in outcomes to justify the very high cost of some regimens. For example, sofosbuvir/daclatasvir, which was the most effective regimen for many cirrhotic patients, had a very high ICER due to its high cost. In probabilistic sensitivity analyses, interferon-free therapy had an ICER <$100 000/QALY in >99% of simulations, and the more effective interferon-free regimen was preferred in >75% of simulations (Supplemental Figure 3).

DISCUSSION

Our analysis demonstrates that interferon-free therapies to treat HCV GT1 provide good value for the resources required to use them broadly in the United States, but they are costly for payers. Cost-control strategies in which noncirrhotic patients are eligible for treatment only when they reach F2 or greater fibrosis do limit cost; however, treating all patients regardless of fibrosis stage results in longer quality-adjusted life-expectancy

Table 3. Cost Effectiveness of Treatment for Hepatitis C Virus Infection Among Genotype 1a and 1b Noncirrhotic Patients Assuming Both "Treat All" and "F2+ Only" Approaches

Treatment Strategy	Cost, $	Incremental Cost, $	QALYs	Incremental QALYs	ICER, $/QALY	SVR, %	Nondiscounted Cost/10 000 Patients, Billion $
Genotype 1a, Treatment-Naive, RNA <6 Million							
No treatment	165 000	-	11.5	-	-	-	0.37
PEG/RBV 48 weeks	206 000	40 800	12.8	1.3	Dominated[a]	43.4	0.84
SOF/LDV 8 weeks treating only F2+	227 000	61 900	14.4	2.9	21 700	88.6	1.02
PEG/RBV/SMV 24 weeks	231 000	3800	13.9	−0.4	Dominated[a]	77.3	1.13
SOF/LDV 8 weeks	233 000	5900	14.6	0.3	22 300	96.2	1.17
PTV/r/OBV/DSV/RBV 12 weeks	252 000	19 000	14.7	0.0	610 000	97.6	1.36
PEG/RBV/SOF 12 weeks	266 000	14 100	14.5	−0.2	Dominated[a]	92.4	1.50
DCV/SOF 12 weeks	329 000	76 500	14.7	0.1	1 520 000	99.1	2.14
Genotype 1a, Treatment-Naive, RNA ≥6 Million							
No treatment	165 000	-	11.5	-	-	-	0.37
PEG/RBV 48 weeks	206 000	41 000	12.8	1.3	Dominated[a]	43.6	0.84
PEG/RBV/SMV 24 weeks	231 000	24 700	13.9	1.1	Dominated[a]	77.2	1.13
PTV/r/OBV/DSV/RBV 12 weeks treating only F2+	243 000	77 900	14.4	2.9	27 100	89.8	1.17
PTV/r/OBV/DSV/RBV 12 weeks	252 000	8900	14.7	0.3	32 600	97.5	1.36
SOF/LDV 12 weeks	261 000	8800	14.6	0.0	Dominated[a]	96.2	1.45
PEG/RBV/SOF 12 weeks	266 000	14 100	14.5	−0.2	Dominated[a]	92.3	1.50
DCV/SOF 12 weeks	329 000	76 500	14.7	0.1	1 400 000	99.1	2.14
Genotype 1a, Treatment-Experienced							
No treatment	156 000	-	11.5	-	-	-	0.39
PTV/r/OBV/DSV/RBV 12 weeks treating only F2+	236 000	80 400	13.9	2.3	Dominated[a]	85.6	1.21
PTV/r/OBV/DSV/RBV 12 weeks	245 000	89 300	14.0	0.2	28 300	95.6	1.39
SOF/LDV 12 weeks	255 000	9500	14.0	0.0	Dominated[a]	94.7	1.48
PEG/RBV/SOF 12 weeks	258 000	13 000	13.9	−0.1	Dominated[a]	92.3	1.52
DCV/SOF 12 weeks	320 000	74 600	14.1	0.1	700 000	98.9	2.15
SMV/SOF 12 weeks	321 000	1500	13.9	−0.3	Dominated[a]	88.4	2.15
Genotype 1b, Treatment-Naive, RNA <6 Million							
No treatment	165 000	-	11.5	-	-	-	0.37
PEG/RBV 48 weeks	206 000	40 700	12.8	1.3	Dominated[a]	43.5	0.84
SOF/LDV 8 weeks treating only F2+	227 000	61 900	14.4	2.9	21 700	88.5	1.02
PEG/RBV/SMV 24 weeks	232 000	5400	14.3	−0.1	Dominated[a]	87.9	1.16
SOF/LDV 8 weeks	233 000	5900	14.6	0.3	22 700	96.1	1.17
PTV/r/OBV/DSV 12 weeks	248 000	14 900	14.7	0.1	182 000	98.4	1.32
PEG/RBV/SOF 12 weeks	266 000	18 400	14.5	−0.2	Dominated[a]	92.4	1.50
DCV/SOF 12 weeks	329 000	80 800	14.7	0.0	4 190 000	99.1	2.14
Genotype 1b, Treatment-Naive, RNA ≥6 Million							
No treatment	165 000	-	11.5	-	-	-	0.37
PEG/RBV 48 weeks	206 000	41 100	12.8	1.3	Dominated[a]	43.5	0.84
PEG/RBV/SMV 24 weeks	232 000	67 200	14.3	2.8	24 400	87.8	1.16
PTV/r/OBV/DSV 12 weeks treating only F2+	239 000	6800	14.4	0.2	Dominated[a]	90.7	1.13
PTV/r/OBV/DSV/RBV 12 weeks	248 000	15 200	14.7	0.4	35 500	98.4	1.32
SOF/LDV 12 weeks	261 000	13 200	14.6	−0.1	Dominated[a]	96.3	1.45
PEG/RBV/SOF 12 weeks	266 000	18 400	14.5	−0.2	Dominated[a]	92.4	1.50
DCV/SOF 12 weeks	329 000	80 800	14.7	0.0	4 470 000	99.1	2.14
Genotype 1b, Treatment-Experienced							
No treatment	156 000	-	10.8	-	-	-	0.39
PTV/r/OBV/DSV/RBV 12 weeks treating only F2+	236 000	80 200	13.7	2.8	Dominated[a]	86.1	1.21
PTV/r/OBV/DSV/RBV 12 weeks	245 000	89 100	14.0	3.2	28 000	96.2	1.39
SOF/LDV 12 weeks	255 000	9800	14.0	0.0	Dominated[a]	94.7	1.48
PEG/RBV/SOF 12 weeks	258 000	13 200	13.9	−0.2	Dominated[a]	92.3	1.52
DCV/SOF 12 weeks	320 000	75 000	14.1	0.1	814 000	99.0	2.15
SMV/SOF 12 weeks	324 000	3700	14.1	0.0	Dominated[a]	98.7	2.19

Abbreviations: DCV, daclatasvir; DSV, dasabuvir; F2, fibrosis stage F2; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; OBV, ombitasvir; PEG, pegylated-interferon; PTV, paritaprevir; QALY, quality-adjusted life year; r, ritonavir; RBV, ribavirin; RNA, ribonucleic acid; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response.

(NOTE: All values are mean per-person values based on Monte-Carlo simulations of 1 000 000 individuals. Nondiscounted cost per 10000 patients is calculated over 5 years. Cost-effectiveness ratios may not match previous columns due to rounding.)

[a]Dominated = strategies more costly and less effective than a competing strategy or strategies with an ICER greater than that of a more effective strategy.

Table 4. Cost-Effectiveness of Treatment for Hepatitis C Virus Infection Among Genotype 1a and 1b Cirrhotic Patients

Treatment Strategy	Cost, $	Incremental Cost, $	QALYs	Incremental QALYs	ICER, $/QALY	SVR, %	Nondiscounted Cost/10 000 Patients, Billion $
Genotype 1a, Treatment-Naive							
No treatment	99 000	-	4.9	-	-	-	0.44
PEG/RBV 48 weeks	158 000	59 600	7.0	2.1	Dominated[a]	23.5	0.91
PEG/RBV/SMV 24 weeks	197 000	38 200	9.9	2.9	Dominated[a]	53.6	1.12
PTV/r/OBV/DSV/RBV 12 weeks	245 000	146 000	13.7	8.9	16 500	92.7	1.36
PEG/RBV/SOF 12 weeks	252 000	6900	12.3	−1.4	Dominated[a]	78.6	1.52
SOF/LDV 12 weeks	255 000	10 000	14.0	0.2	43 000	95.1	1.45
DCV/SOF 24 weeks	453 000	198 000	14.1	0.1	2 370 000	96.9	3.46
Genotype 1a, Treatment-Experienced							
No treatment	99 000	-	4.7	-	-	-	0.47
PEG/RBV/SOF 12 weeks	246 000	147 000	11.5	6.8	Dominated[a]	78.3	1.54
SOF/LDV/RBV 12 weeks	253 000	154 000	12.9	8.2	18 700	94.2	1.53
PTV/r/OBV/DSV/RBV 24 weeks	315 000	62 100	12.8	−0.1	Dominated[a]	94.0	2.17
SMV/SOF 12 weeks	317 000	64 500	12.5	−0.4	Dominated[a]	90.0	2.21
SOF/LDV 24 weeks	334 000	81 000	13.0	0.2	520 000	96.8	2.34
DCV/SOF/RBV 24 weeks	453 000	119 000	13.0	0.0	Dominated[a]	96.7	3.56
Genotype 1b, Treatment-Naive							
No treatment	99 000	-	4.9	-	-	-	0.44
PEG/RBV 48 weeks	158 000	59 400	7.0	2.10	Dominated[a]	23.1	0.91
PEG/RBV/SMV 24 weeks	205 000	46 800	10.8	3.80	Dominated[a]	62.4	1.15
PTV/r/OBV/DSV/RBV 12 weeks	248 000	149 000	14.2	9.27	16 100	97.0	1.37
PEG/RBV/SOF 12 weeks	252 000	4000	12.4	−1.79	Dominated[a]	78.5	1.52
SOF/LDV 12 weeks	255 000	7100	14.0	−0.17	Dominated[a]	95.3	1.45
DCV/SOF 24 weeks	453 000	205 000	14.1	−0.10	Dominated[a]	96.9	3.46
Genotype 1b, Treatment-Experienced							
No treatment	98 000	-	4.6	-	-	-	0.46
PTV/r/OBV/DSV/RBV 12 weeks	239 000	141 000	13.0	8.40	16 800	96.3	1.38
PEG/RBV/SOF 12 weeks	245 000	5800	11.4	−1.59	Dominated[a]	78.3	1.54
SOF/LDV/RBV 12 weeks	252 000	12 600	12.8	−0.21	Dominated[a]	94.0	1.52
SMV/SOF 12 weeks	319 000	79 700	13.1	0.10	828 000	97.4	2.19
SOF/LDV 24 weeks	332 000	13 500	13.0	−0.16	Dominated[a]	96.4	2.34
DCV/SOF/RBV 24 weeks	451 000	132 000	12.9	−0.18	Dominated[a]	96.2	3.56

Abbreviations: DCV, daclatasvir; DSV, dasabuvir; F2, fibrosis stage F2; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; OBV, ombitasvir; PEG, pegylated-interferon; PTV, paritaprevir; QALY, quality-adjusted life year; r, ritonavir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response.

(NOTE: All values are mean per-person values based on Monte-Carlo simulations of 1 000 000 individuals. Nondiscounted cost per 10 000 patients is calculated over 5 years. Cost-effectiveness ratios may not match previous columns due to rounding.)

[a]Dominated = strategy is more costly and less effective than a competing strategy or strategies with an ICER greater than that of a more effective strategy.

(between 0.2 and 0.3 QALYs) and is cost effective. If seeking rational cost control, payers should focus on price negotiations rather than treatment restrictions. At this time, with multiple interferon-free treatment options available, there are HCV treatment regimens that remain appealing to providers, but they are not cost effective. In treatment-naive, noncirrhotic patients with low viral load, for example, who are eligible for an 8-week course with sofosbuvir/ledipasvir, choosing a 12-week regimen in hope of gaining treatment efficacy is not cost effective. It will be possible to attain better population-level outcomes by negotiating best prices and treating the greatest number possible, even if the preferred first-line regimen is somewhat less effective than another option.

Our work should be read in context of a growing body of literature. We independently confirm that (1) interferon-free options are cost effective [2–4] and that (2) treating early stage disease is preferred to F2+ only approaches [5, 6]. The analysis extends those findings by determining the value of small improvements in efficacy in treatment-naive patients. We find that among competing regimens with efficacy >90%, cost should be the primary driver of formulary decisions. Negotiating prices and limiting formulary for noncirrhotic patients is a better approach to cost control than current disease stage treatment restrictions. To our knowledge, this paper provides one of the first quantitative comparisons of cost-control options.

This analysis has several limitations. First, our finding that F2+ only strategies are not preferred depends in part on assumptions about QoL with early stage HCV. Utility values are difficult to estimate and are imprecise. In sensitivity analyses, however, we identified the threshold utility value that results in treat F2+ only becoming preferred. We note that the threshold value (0.97) is substantially higher than base case (0.89) and higher

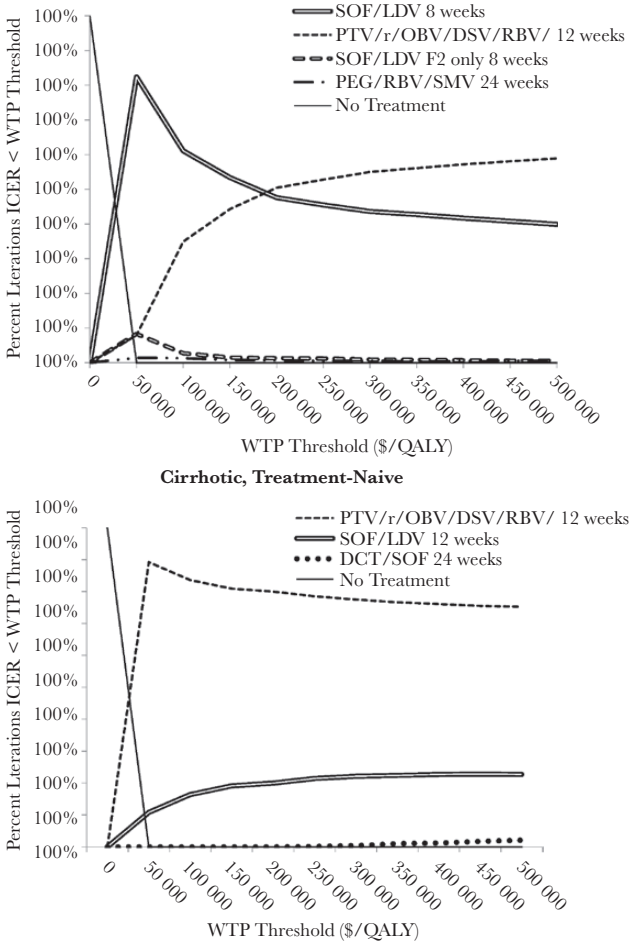

Figure 1. Cost-effectiveness acceptability curves for the treatment of hepatitis C virus (HCV) genotype 1b patients with and without cirrhosis. Each panel presents the results of probabilistic sensitivity analyses in which we performed multiple iterations of the cost-effectiveness simulation, each time drawing treatment efficacy parameters from defined probability density functions. The horizontal axis represents increasing societal willingness to pay thresholds. Each line represents a treatment strategy. For clarity, we excluded those strategies where the incremental cost-effectiveness ratio (ICER) was above a willingness-to-pay (WTP) threshold of $500 000 in >99% of iterations. The vertical axis depicts the percentage of the simulation iterations in which a given strategy was "preferred" from a cost-effectiveness perspective at a given societal willingness to pay. All costs are in 2014 US dollars and discounted at an annual rate of 3%. DCV, daclatasvir; DSV, dasabuvir; LDV, ledipasvir; OBV, ombitasvir; PTV, paritaprevir; QALY, quality-adjusted life year; r, ritonavir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.

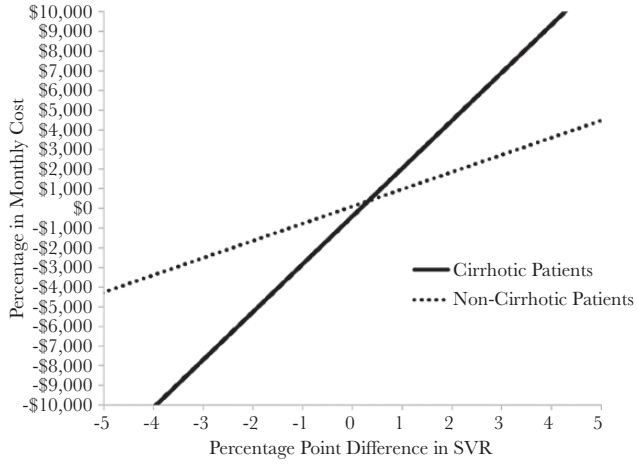

Figure 2. Two-way sensitivity analysis on interferon-free regimen efficacy and cost. The analysis holds the efficacy and cost of 1 interferon-free treatment ("regimen A") constant, while varying the efficacy and cost of a competing interferon-free regimen ("regimen B"). To improve generalizability such that the analysis applies to future interferon-free treatment options, we defined the ranges of drug cost and efficacy based on those of current competing drugs, but the analysis is not based on a single regimen. The horizontal axis depicts the relative efficacy of regimen B compared with regimen A. The vertical axis depicts the relative cost. Each line depicts the threshold cost that results in regimen B having an incremental cost-effectiveness ratio (ICER) <$100 000/quality-adjusted life year compared with regimen A at the given relative efficacy. The slope of the line thus represents the economic value of an additional percentage point increase in treatment efficacy. The solid line represents cirrhotic patients, and the dotted line represents noncirrhotic patients. All costs are in 2014 US dollars and discounted at an annual rate of 3%. SVR, sustained virologic response.

than most reports in the literature [14]. Readers can use these results to calibrate conclusions with any emerging data about QoL. Second, similar to other cost-effectiveness analyses [2–4], our efficacy inputs are based on clinical trials and not real-world effectiveness. For instance, if twice-daily regimens are less effective than indicated in efficacy trials, whereas single tablet, once daily regimens are similar, then costly once daily regimens could appear to be economically attractive. However, our sensitivity analyses demonstrate that among noncirrhotic patients, the gap in treatment effectiveness would need to be large to justify the substantially higher price: for example, a large gap of 5% better effectiveness would only support $4000 in increased price. In addition, we also use the clinical trials to inform model demographics, which may be different from the general HCV population, although our conclusions do not change in our sensitivity analyses varying age, mortality, and QoL (all of which may differ with demographics) (Supplemental Tables 4, 5, 13, 14). Third, because knowledge of the optimal combination of available medications to treat HCV is evolving, this analysis excludes treatment regimens recently approved. For instance, we did not include recommended regimes of elbasvir/grazoprevir or sofosbuvir/velpatasvir [42]; however, this approach is unlikely to be significantly different from other highly efficacious regiments. Likewise, our analysis was completed shortly before the US Food and Drug Administration issued a "black box warning" about the use of paritaprevir/ritonavir/ombitasvir/dasabuvir in patients with advanced liver disease [43]. Nevertheless, we demonstrate that tradeoffs between price and efficacy will be relevant to considering the cost effectiveness of these future regimens compared with the current standard of care. Fourth, because discounts negotiated with pharmaceutical companies typically include a nondisclosure agreement, it is not possible to know what each payer pays for HCV medications. In the base case, we assumed an average discount of 23% off of AWP, and we explored that cost in extensive sensitivity analysis (Supplemental Tables 11–12). Fifth, although we

account for increased costs and mortality and decreased utility of advancing liver disease, we did not model specific manifestations of this such as hepatocellular carcinoma, liver transplantation, or other extrahepatic consequences of HCV. Modeling these effects separately would not change our overall results, but it may be beneficial for stakeholders who want to find another way to quantify the effect of treatment on health outcomes. Sixth, although we assumed that fibrosis progression halts after SVR, some studies suggest that progression may continue at a much slower rate or that fibrosis would regress instead. In sensitivity analysis where patients were subject to lower QoL after SVR (if progression continued, for example), our conclusions were unchanged, although the ICERs increased. The effect of fibrosis regression is not well understood in the literature, although if present we would expect treatment to become more attractive and for ICERs to fall given the additional benefit of regression. In addition, our model assumed a linear progression through fibrosis stages with a 25-year median time to cirrhosis among the cohort. More recent literature suggests that fibrosis progression is not linear, with faster progression through early stages of disease [44]. However, the main driver of cost-effectiveness conclusions in the model was the time to becoming cirrhotic. We experimented with a broad array of median times to cirrhosis, and we found that our conclusions are consistent. Seventh, our analysis assumed a healthcare system perspective that included the costs of medical care (HCV and non-HCV), but it did not include costs related to lost labor productivity and disability. Were we to incorporate those costs in the model, the net cost of HCV therapy would be less, although it is difficult to imagine a scenario in which preventing disability provides so much benefit as to entirely offset the high cost of treatment. Finally, we assumed that competing risks of death for HCV-infected patients initiating therapy are similar to those of the general US population. If history of substance use or other risk factors that led to HCV infection also have an impact on long-term mortality, then the cost-effectiveness ratios of treatment may be higher than those reported.

CONCLUSIONS

New therapies to treat HCV GT1 have changed the paradigm of HCV care from chronic, moderately effective disease management to short-term, curative therapy [45]. Our analysis demonstrates that expanding treatment access, including to patients with early stage disease, will improve clinical outcomes and is cost effective, but it will have a very high cost. Currently, many payers restrict access to HCV therapy based on fibrosis stage [9, 46], and although some have been forced to relax restrictions through litigation [47], these policy changes are occurring without clear evidence of the right cost-control measures and without knowledge of the long-term consequences of these policies on human health and local budgets. We show that such strategies are not the best approach to control spending on HCV treatment from the perspective of the health system. We also find that lower drug costs for interferon-free regimens to treat noncirrhotic patients in a competitive drug market will improve cost effectiveness and reduce short-term payer costs, suggesting that payers should focus on price negotiations as a cost-control strategy. Now that there are multiple effective HCV regimens and there is greater competition in this market, it is important to expand efforts to identify and treat patients with chronic HCV infection in the United States.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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